SOY ISOFLAVONES IN PROSTATE CANCER PREVENTION, TREATMENT AND SURVIVORSHIP RESEARCH

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(a) Prostate cancer incidence (b) Prostate cancer mortality
## Prostate cancer incidence and mortality worldwide

### Prostate Cancer Incidence and Mortality Worldwide in 2008 – Summary

<table>
<thead>
<tr>
<th>Estimated numbers (thousands)</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>899</td>
<td>258</td>
</tr>
<tr>
<td>More developed regions</td>
<td>644</td>
<td>136</td>
</tr>
<tr>
<td>Less developed regions</td>
<td>255</td>
<td>121</td>
</tr>
<tr>
<td>WHO Africa region (AFRO)</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>WHO Americas region (PAHO)</td>
<td>334</td>
<td>76</td>
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<tr>
<td>WHO East Mediterranean region (EMRO)</td>
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<td>9</td>
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<tr>
<td>WHO Europe region (EURO)</td>
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<td>94</td>
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<tr>
<td>WHO South-East Asia region (SEARO)</td>
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<td>19</td>
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<td>WHO Western Pacific region (WPRO)</td>
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<tr>
<td>IARC membership (22 countries)</td>
<td>611</td>
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<tr>
<td>United States of America</td>
<td>186</td>
<td>28</td>
</tr>
<tr>
<td>China</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>India</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>European Union (EU-27)</td>
<td>323</td>
<td>71</td>
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</table>
Soy isoflavones and cancer

• Epidemiologic studies show an inverse association between dietary soy intake and cancer risk (breast, prostate, lung, and others)
• **Genistein** and daidzein are the most abundant isoflavones in soy
• **Genistein** has activity against a variety of cancer cells in culture, animal model and clinical studies
Soy Isoflavones

A. Tamoxifen

B. Genistein

C. Estradiol (E2)
Genistein and Cancer

- Inhibits growth and induces apoptosis in Ca cells
- Growth inhibition mediated by G2/M cell cycle arrest and up-regulation of p21WAF1
- Down-regulates cyclin B1, CDKs, Bcl-2/Bcl-xL
- Up-regulates Bax expression and induces translocation of Bax to Mitochondria
Genistein

- Down-regulates MMP-2, MMP-9, uPA, c-IAP and VEGF
- Inactivates Akt and NF-κB (by inhibiting IKK)
  - blocks nuclear translocation of p50 and p65
  - inhibits phosphorylation of IκBa
  - decreases MEKK1 kinase activity
Genistein and PC3 Proliferation
Apoptosis assay for PC3 cells treated with genistein, docetaxel, cisplatin, adriamycin, or combination

Con: Control; G: genistein; D: docetaxel; Cis: cisplatin; A: adriamycin
G+D: genistein followed by docetaxel; G+Cis: genistein followed by cisplatin.
G+A: genistein followed by adriamycin.

*: $p < 0.01$
Growth inhibition in PC3 cells treated with genistein, docetaxel, or combination measured by MTT

G: treated with 50 mM genistein for 48h;  
D: treated with 1nM docetaxel for 48h;  
G+D: treated with 30 mM genistein for 24h followed by 0.5 nM docetaxel for 24h.  
*: p < 0.05
EMSA for NF-κB activity in PC3 cells treated with docetaxel or cisplatin

<table>
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<th>2 nM Docetaxel</th>
<th>300 nM Cisplatin</th>
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<tr>
<td>2h</td>
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<tr>
<td>8h</td>
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[Image of EMSA gel showing bands for different treatments and time points]
EMSA for NF-κB activity in BxPC-3 cells treated with genistein, cisplatin, or combination

<table>
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<tr>
<th>Supershift</th>
<th>Non-specific competitor</th>
<th>Specific competitor</th>
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<tr>
<td></td>
<td>Control</td>
<td>25nM Cis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50nM Cis</td>
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<tr>
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<td>100nM Cis</td>
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<tr>
<td></td>
<td></td>
<td>20μM Gen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50μM Gen</td>
</tr>
<tr>
<td></td>
<td>20μM Gen &amp; 25nM Cis</td>
<td>20μM Gen &amp; 50nM Cis</td>
</tr>
<tr>
<td></td>
<td>20μM Gen &amp; 100nM Cis</td>
<td>20μM Gen &amp; 100nM Cis</td>
</tr>
</tbody>
</table>

Cis: cisplatin; Gen: genistein.
Genistein is Safe when Combined with XK469 (n = 3 donors)

Figure 2. Three human bone marrows were processed to isolate the mononuclear cells, which were stimulated with rGM-CSF to produce clonogenic colonies of neutrophils and monocytes called CFU-GM. Toxicity of the investigational drug XK469 was quantified from inhibition of CFU-GM colony formation. The presence of 10-20 microM genistein did not change the potency of the toxic action of XK469 upon these hematopoietic cells.
NFkB

Degradation
Ubiquitin-Proteasome

Growth Factor, Cytokine

NIK \rightarrow IKK \rightarrow Akt

I kB

Genistein

Active NFkB

Nuclear Translocation

Transcription

- cIAP-1, XIAP, MMP-9, uPA, VEGF, etc.

A

![Graph showing tumor volume over days for control, prevention, and intervention groups. The graph indicates a significant difference between groups with p values 0.0001 and 0.0003.]

B

![Images labeled control and prevention showing differences in tumor appearance.]

C

![Images labeled control and prevention showing differences in tumor appearance.]

$p = 0.0001$

$p = 0.0003$
Fig-8: Genistein enhanced PC-3 bone tumor growth inhibition induced by docetaxel.  

A: Inhibitory effects of genistein and/or docetaxel on the growth of bone tumors formed by PC-3 cells in SCID-human mice. 

B: Comparison of the tumor volumes in each group on the day when all mice were sacrificed. (*: p<0.01, Genistein vs Control, Docetaxel vs Control, Genistein+Docetaxel vs Control; ♦: p=0.01, Genistein+Docetaxel vs Docetaxel). 

C: Ex vivo bone tumor X-ray showed more osteolysis and tumor growth in control group (a) than in genistein treatment group (b).

Fig-9: OPG expression was up-regulated by genistein and down-regulated by docetaxel.  

A: Real-time RT-PCR analysis of OPG mRNA expression in genistein or docetaxel treated PC-3 cells. 

B: Real-time RT-PCR melting curve showing the PCR product of OPG is pure (only one peak). 

C: Western Blot analysis of OPG protein expression in genistein and/or docetaxel treated PC-3 cells (C: Control; G: 50 μM Genistein treatment; D: 2 nM Docetaxel treatment; G+D: 30 μM Genistein and 1 nM docetaxel combination treatment).

Li Y et al. Cancer Res. 2006
Genistein down-regulated expression and secretion of RANKL and inhibited osteoclast differentiation. A: Western Blot analysis showed that 50 μM genistein inhibited the expression of RANKL and abrogated TNF-α (100 ng/ml) induced expression of RANKL in PC-3 cells. B: Western Blot analysis showed that genistein significantly inhibited the secretion of RANKL in RANKL transfected PC-3 cells.

MMP-9 activity assay showed that genistein significantly inhibited activity of MMP-9 secreted by RANKL-transfected PC-3 cells. C: Genistein inhibited RANKL-induced RAW264.7 cell differentiation to osteoclasts. The multinucleated osteoclasts were observed. (a. control, no RANKL added; b. treated with 100 ng/ml RANKL; c. treated with 100 ng/ml RANKL and 10 μM genistein; d. treated with 100 ng/ml RANKL and 0.5 nM docetaxel; e. treated with 100 ng/ml RANKL, 10 μM genistein, and 0.5 nM docetaxel; x200). D: Genistein inhibited RANKL-induced RAW264.7 cell differentiation to osteoclasts (TRAP staining; x200). In figures a to e, tartrate was added during staining. Multi-nuclei and purplish to dark red granules were observed only in osteoclasts. (a. control, no RANKL added; b. treated with 100 ng/ml RANKL; c. treated with 100 ng/ml RANKL and 10 μM genistein; d. treated with 100 ng/ml RANKL and 0.5 nM docetaxel; e. treated with 100 ng/ml RANKL, 10 μM genistein, and 0.5 nM docetaxel). In figure f, no tartrate was added during TRAP staining. The purplish granules indicated total acid phosphatase (tartrate-resistant and tartrate-sensitive acid phosphatase). RAW264.7 cells contain tartrate-sensitive acid phosphatase. E: Graph showed the ratio of tartrate-sensitive acid phosphatase versus total acid phosphatase. The value indicated the comparative amount of osteoclasts in each sample.
Fig-14: MMP-9 expression was up-regulated by docetaxel and down-regulated by genistein. A: Real-time RT-PCR analysis of MMP-9 mRNA expression in genistein or docetaxel treated PC-3 cells. B: Real-time RT-PCR melting curve showing the PCR product of MMP-9 is pure (only one peak). C: Western Blot analysis of MMP-9 protein expression in genistein and/or docetaxel treated PC-3 cells (C: Control; G: 50 μM Genistein treatment; D: 2 nM Docetaxel treatment; G+D: 30 μM Genistein and 1 nM docetaxel combination treatment). D: Western Blot analysis of MMP-9 protein expression in genistein or docetaxel treated PC-3 cells with or without MMP-9 siRNA transfection. E: MMP-9 activity assay showed that MMP-9 was up-regulated by docetaxel and down-regulated by genistein in PC-3 cell lysate and conditioned medium. F: MMP-9 activity assay showed that MMP-9 was up-regulated by docetaxel and down-regulated by genistein in conditioned medium of PC-3 cell and RANKL induced RAW264.7 cell co-culture.
Fig-11: Genistein potentiated docetaxel-induced inhibition of PC-3 cell invasion. A: Invasion assay showed that combination treatment of genistein and docetaxel significantly inhibited the invasion of PC-3 cells through matrigel matrix membrane in PC-3 growth (a to d) or differentiated osteoclast growth (e to i) environment. (a. control; b. treated with 50 nM genistein; c. treated with 2 nM docetaxel; d. treated with 50 nM genistein and 1 nM docetaxel; e. control, no RANKL added; f. treated with 100 ng/ml RANKL; g. treated with 100 ng/ml RANKL and 50 nM genistein; h. treated with 100 ng/ml RANKL and 2 nM docetaxel; i: treated with 100 ng/ml RANKL, 50 nM genistein, and 1 nM docetaxel; x200). B: The graphs showed the value of fluorescence from the invaded PC-3 cells. The value indicated the comparative amount of invaded PC-3 cells.

Li Y et al. Cancer Res. 2006
Effect of Dietary Genistein on MMP Gene Expression in Experimental Metastasis

Prevention with genistein/Control diet

Intervention with genistein/Control diet

PC3 bone tumor/PC3 subcutaneous tumor

Z48481 Homo sapiens membrane-type matrix metalloproteinase 1
NM_004530.1 Homo sapiens matrix metalloproteinase 2
NM_004995.2 Homo sapiens matrix metalloproteinase 14
NM_005940.2 Homo sapiens matrix metalloproteinase 11
NM_004994.1 Homo sapiens matrix metalloproteinase 9
NM_002421.2 Homo sapiens matrix metalloproteinase 1
NM_002426.1 Homo sapiens matrix metalloproteinase 12
NM_002427.2 Homo sapiens matrix metalloproteinase 13
NM_004142.1 Homo sapiens matrix metalloproteinase-like 1

Decrease Increase

PC3 cells treated with genistein/No genistein treatment

NM_004994.1 Homo sapiens matrix metalloproteinase 9

Affymetrix Human Genome U95 or U133A Array
Cluster Analysis According to Biological Function

Numbers of altered genes in different categories in PC3 bone tumors after genistein treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Up</th>
<th>Down</th>
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<tbody>
<tr>
<td>apoptosis</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>cell cycle arrest, negative regulation of cell proliferation and transcription</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>signal transduction, chemotaxis</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>regulation of transcription and protein biosynthesis</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>oncogenesis</td>
<td>8</td>
<td>4</td>
</tr>
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</table>
Effects of genistein on gene expression

*Based on in vitro and in vivo gene profiling with and without genistein*
Plot of predicted rise in log PSA with time
Treatment of PC-3 Prostate Tumors with Radiation + Genistein in Nude Mice

Mean Tumor Volume (mm³)

- Control
- Genistein
- Radiation
- Rad+Gen
Genistein-Radiation Pilot Study

- 42 patients with prostate cancer
- Randomized, placebo-controlled, phase 2 study
- 20 patients received soy isoflavones 200 mg/day for 3 months, starting with the first day of radiation, and 22 received placebo
- QOL questionnaires given at 3 and 6 months
## Study Patients

<table>
<thead>
<tr>
<th>Group 1 (Soy)</th>
<th>Group 2 (Placebo)</th>
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<tbody>
<tr>
<td><strong>Median Age = 60 y</strong></td>
<td><strong>Median Age = 65 y</strong></td>
</tr>
<tr>
<td>8 T1c, 3 T2a, 2 T2b</td>
<td>10 T1c, 2 T2a, 1 T2b</td>
</tr>
<tr>
<td><strong>Median Pre PSA</strong></td>
<td><strong>Median Pre PSA</strong></td>
</tr>
<tr>
<td>3.7</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>Median 4-6 month PSA</strong></td>
<td><strong>Median 4-6 month PSA</strong></td>
</tr>
<tr>
<td>0.9</td>
<td>2</td>
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<tr>
<td><strong>PSA decrease</strong></td>
<td><strong>PSA decrease</strong></td>
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<td>75.7%</td>
<td>59.2%</td>
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# Genitourinary (GU) Toxicity

<table>
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<tr>
<th>Soy</th>
<th>3M n=13</th>
<th>6M n=13</th>
<th>Placebo</th>
<th>3M n=13</th>
<th>6M n=14</th>
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<tr>
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<td><strong>GU toxicity</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Leakage/Dripping of Urine</td>
<td>15.4% (2)</td>
<td>7.7% (1)</td>
<td>Leakage/Dripping of Urine</td>
<td>23.1% (3)</td>
<td>28.6% (4)</td>
</tr>
<tr>
<td>Big/Medium Problem with Frequency</td>
<td>38.5% (5)</td>
<td>0%</td>
<td>Big/Medium Problem with Frequency</td>
<td>38.5% (5)</td>
<td>7.1% (1)</td>
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<tr>
<td>Big/Medium Problem with Urgency</td>
<td>30.8% (4)</td>
<td>0%</td>
<td>Big/Medium Problem with Urgency</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Function same as before RT or Better</td>
<td>92.3% (12)</td>
<td>92.3% (12)</td>
<td>Function same as before RT or Better</td>
<td>92.3% (12)</td>
<td>85.7% (12)</td>
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## Erectile Function

<table>
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<tr>
<th>Soy</th>
<th>3 M (n=13)</th>
<th>6 M (n=13)</th>
<th>Placebo</th>
<th>3 M (n=13)</th>
<th>6 M (n=14)</th>
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<tbody>
<tr>
<td><strong>Erectile Function</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ability to Have Full Erections</td>
<td>69.2% (9)</td>
<td>77% (10)</td>
<td>Ability to Have Full Erections</td>
<td>61.5% (8)</td>
<td>57.1% (8)</td>
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<tr>
<td>Reduction in Ability to Have Erections</td>
<td>15.4% (2)</td>
<td>15.4% (2)</td>
<td>Reduction in Ability to Have Erections</td>
<td>46.2% (6)</td>
<td>57.1% (8)</td>
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<tr>
<td>Function Same as Before RT or Better</td>
<td>84.6% (11)</td>
<td>84.6% (11)</td>
<td>Function Same as Before RT or Better</td>
<td>61.5% (8)</td>
<td>57.1% (8)</td>
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Effects of Genistein on CpG Methylation and Histone Acetylation Have Been Reported From Several Groups
Wnt Pathway Inhibitory Genes are hypermethylated in prostate cancer patients

<table>
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<tr>
<th></th>
<th>SOX7</th>
<th>WIF1</th>
<th>SFRP1</th>
<th>DKK3</th>
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<td>PT30</td>
<td>U</td>
<td>M</td>
<td>U</td>
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Whole Genome Expression Profiling Of Prostate Cancer Cells Treated with Genistein

Genistein Upregulates Genes Involved in Cell Cycle Responses to DNA Damage
Genistein Downregulates Genes Involved in the TNF-NFκB Pathway
Genistein induces Acetylation of Histone H3K9

Anti-Ac-H3K9 Chromatin Immunoprecipitation

Genistein induces expression of HAT1

Histone Acetyl Transferase 1 (HAT1)

Genistein synergizes with HDACi Vorinostat to inhibit proliferation

Genistein synergizes with HDACi Vorinostat to induce apoptosis

Whole Genome Expression Profiling Of Prostate Cancer Cells Treated with Genistein, Vorinostat, or Genistein plus Vorinostat

Genistein/Vorinostat Upregulates Genes Involved in Cell Cycle Responses to DNA Damage

<table>
<thead>
<tr>
<th>GO Term</th>
<th>Biological Process</th>
<th>Count</th>
<th>p-value</th>
<th>IPA Biological Function</th>
<th>Count</th>
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<tr>
<td>GO:0006281</td>
<td>DNA repair</td>
<td>45</td>
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<tr>
<td>GO:0008219</td>
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<td>Cell Death</td>
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<tr>
<td>GO:0022403</td>
<td>Cell Cycle</td>
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<td>Cell Cycle</td>
<td>105</td>
<td>2.70E-09</td>
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<tr>
<td>GO:0006915</td>
<td>Apoptosis</td>
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<td>1.37E-03</td>
<td>Apoptosis</td>
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<tr>
<td>GO:0000075</td>
<td>Cell Cycle Checkpoint</td>
<td>17</td>
<td>1.45E-06</td>
<td>DNA checkpoint control</td>
<td>13</td>
<td>1.90E-06</td>
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</table>
AMPK and PPAR agonists are exercise mimetics


• Natural compounds may mimic or potentiate the effects of exercise and may prevent the development of metabolic syndrome:
  – Natural compounds, such as genistein, have endurance-enhancing activities, but their exact mechanisms remain unclear

• Studied endurance capacities of mice in a treadmill running test.

• PPAR agonist and exercise training synergistically increased myofibers and running endurance in adult mice.

• In sedentary mice, 4 weeks of treatment with an AMPK agonist induced metabolic genes and enhanced running endurance by 44%.
Genistein improves cardiovascular risk factors


54 mg genistein + Ca + vitamin D, was associated with favorable effects on glycemic control and cardiovascular risk markers
Genistein vs Placebo

Citracal plus Genistein

Citracal (Calcium + Vit D)
Genistein, insulin sensitivity and memory


In aged ovariectomized female rats

GENISTEIN

increased insulin sensitivity

improved spatial memory
Soy isoflavones, but not Premarin, attenuated AD-relevant protein phosphorylation in primate brain.

Epitopes assessed:
- PHF-1
- Tau-1

(from H Kim et al., 2001, BioFactors)
Relationship between neuroprotective actions by soy versus estrogen

Soy?

Hyperphosphorylated tau

Depolymerized microtubules; (dysfunctional neuron)

Stable microtubule; (viable neuron)

Kim, 2001
Principal Component Analysis indicates that soy+, soy- and casein-based diets, had non-overlapping global effects on brain proteins.
Isoflavones and cognitive function in older women: the Soy and Postmenopausal Health In Aging (SOPHIA) Study

6-month, double-blind, randomized, placebo-controlled clinical trial

Study subjects were in good health, postmenopausal and not using estrogen replacement therapy

Randomized to active treatment (n = 27) two pills per day, each containing 55 mg of soy-extracted isoflavones (110 mg per day) or placebo (n = 26).

Cognitive function tests administered at baseline and follow-up included: Trails A and B, category fluency, and logical memory and recall (a paragraph recall test assessing immediate and delayed verbal memory).

Kritz-Silverstein D; Von Muhlen D; Barrett-Connor E; Bressel M. Menopause. 10:196-202, 2003.
Isoflavones and cognitive function in older women: Soy & Postmenopausal Health In Aging (SOPHIA) Study.

At baseline, all women were cognitively intact; there were no significant differences by treatment assignment in age, education, depressed mood, or cognitive function (all P values > 0.10).

The women in the treatment group did consistently better, both as compared with their own baseline scores and as compared with the placebo group responses at 6 months.

Comparisons of percentage change in cognitive function between baseline and follow-up showed greater improvement in category fluency for women on active treatment as compared with the case of those on placebo (P = 0.02) and showed greater improvement on the other tests of verbal memory and Trails B.
Soy isoflavones ameliorate the adverse effects of chemotherapy in children


- 9 cycles of chemotherapy were administered without genistein, and 57 cycles with genistein (8 mg/day).
- Patients had less myelosuppression, mucositis, and infection when they received their chemotherapy with genistein.
- During supplementation, serum genistein levels were 2-6 times higher compared to presupplementation levels.
- Patients who received abdominal radiation reported less pain and diarrhea when they took the genistein supplement.
Summary

• Genistein
  – Antioxidant (prevents DNA damage)
  – Anti-inflammatory (IL-1, IL-6 inhibition)
  – DNA demethylation
  – Histone acetylation
  – NFkB, RANKL, VEGF, MMP, EMT inhibition
  – Enhances chemo/RT
  – Reduces toxicities of chemo/RT
  – Potentiates immune function (anti-viral, anti-bacterial)
Genistein in survivorship research

- **Opportunities for prevention of short term and long term adverse effects** of radiation and chemotherapy:
  - Second primary tumors
  - Cognitive decline
  - Cardiac toxicity
  - Myelosuppression
  - Pulmonary toxicity
  - Neurotoxicity (CNS and peripheral neuropathy)
  - Nephrotoxicity
  - Hepatotoxicity

- **Improved efficacy** of chemo/RT and targeted therapy
- **Genistein** is a *safe*, *orally bioavailable* compound which has been *well tolerated* in clinical trials
Let food be your medicine.
Hippocrates

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